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Glucagon-Like Peptide-1s Compared to Sulfonylureas in the Treatment of Adults Diagnosed with Type II Diabetes Mellitus in Primary Care

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Abstract

Type II diabetes mellitus (T2DM) is a prevalent disease in our country. Bullard et al. (2018) report approximately 21 million adults have T2DM in the United States. "The total estimated cost of diagnosed diabetes in 2017 is $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity" (Yang et al., 2018). Treatment of T2DM is individualized to each patient based on their co-morbidities, fiscal responsibility, and route of administration options. Sulfonylureas and Glucagon-like Peptide-1s (GLP-1) are two classes of antidiabetic drugs that are available for use as second line treatment options after metformin. This review of literature is from articles published in 2008 or later found in the following electronic databases: PubMed, Cochrane Database of Systematic Reviews, DynaMed Plus, ClincalKey, and Scopus. Articles included randomized control trials, systematic reviews, and meta analyses with participants being at least eighteen years old. The review found several benefits of GLP-1s for the treatment of T2DM. The risks of GLP-1s are not found to be as serious as the risks associated with sulfonylureas. Sulfonylureas demonstrate historical data for their use and are available in oral forms as opposed to GLP-1s which is newer but in an injectable form only. Overall, GLP-1s offer greater benefits with minimal side effects that are less severe than sulfonylureas. Limitations to this literature review include lack of articles having direct reviews of GLP-1s and sulfonylureas.

Keywords: glucagon-like peptide-1, sulfonylurea, diabetes mellitus, second line treatment

Introduction

- The National Institute of Diabetes and Digestive and Kidney Diseases (n.d.) defines type II diabetes mellitus (T2DM) as a chronic condition that affects the way your body is able to metabolize glucose.
- With T2DM, the body is not able to maintain a normal glucose level which affects multiple other body systems.
- Since there is no cure for diabetes, patients will need to control their blood glucose levels with diet and exercise. If that is not successful, antidiabetic drugs are utilized to supplement the body.
- Each drug class acts on the body in a different way to achieve their effects. Due to the difference in mechanisms of actions of each drug, there are different benefits and risks of the drug classes.
- The purpose of this review is to determine if sulfonylureas or GLP-1s offer more benefits while minimizing the adverse effects for second line treatment of adults with T2DM in the primary care setting.

Statement of Problem

With an increasing number of patients getting diagnosed with T2DM and newer drugs being developed, selecting an appropriate drug that offers the most benefit for the patient can be overwhelming. Further research is needed to identify which antidiabetic medication effectively lowers the A1c while providing additional benefits with minimal risks such as hypoglycemia.

Research Question

In adult patients with uncontrolled T2DM in the primary care setting, does treatment with GLP-1s compared to sulfonylureas as adjuvant therapy to metformin offer more benefits while minimizing adverse effects?

Literature Review

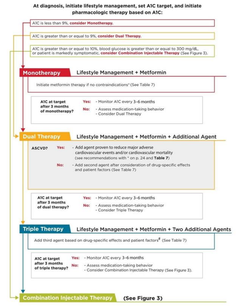

Figure 1. Reprinted from *Standards of medical care in diabetes – 2018 abridged for primary care providers*, by American Diabetes Association (2018), retrieved from http://clinical.diabetesjournals.org/content/36/1/14.full-text.pdf Copyright 2018 by American Diabetes Association.

Current Treatment Guidelines for Adults with T2DM

In the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review in 2016 (Maruthur et al., 2016)

- Metformin plus exenatide (GLP-1) was the preferred combination to lower the hemoglobin A1c (based on 3 short duration trials, pooled between group difference 0.26%, 95% CI 0.03%-0.48%).
- When considering body weight, metformin plus a GLP-1 was preferred (based on 4 trials, not pooled due to differences in dosing, drug type, and study duration; range of between group differences 2.4-12.3 kg).
- Second line treatment to reduce major cardiovascular events and mortality:
  - If ASCVD is present, GLP-1s such as empagliflozin or liraglutide are strongly recommended by the ADA (American Diabetes Association, 2018).
  - If ASCVD is not present and A1c is not at goal, there is an ADA grade A recommendation for dual therapy, which should be selected based on patient factors and drug characteristics.

Montivida, Shaw, Atherton, Stringer, and Paul (2016)

- Sulfonylureas were the most popular second-line treatment. GLP-1 usage for second-line treatment increased in 2016. GLP-1 initiation was at the highest body mass index levels of all second-line treatment options.
- Limitations: lack of information on adherence, side effects, dosage changes, socioeconomic status, and insurance type.

Table 1

Antidiabetic treatment medications and patient considerations for T2DM

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of CKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Canagliflozin: not recommended with eGFR <45 • Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 • Empagliflozin: contraindicated with eGFR <30	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA, UTI, yeast infections, rare in T2DM • Genitourinary infections • Risk of severe dyslipidemia, hypovolemia • ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral; Semaglutide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	• Exenatide: not indicated with eGFR <30 • Lixisenatide: caution with eGFR <30 • Increased risk of side effects in patients with renal impairment	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects (nausea, vomiting, diarrhea) • Injection site reactions • Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required; can be used in renal impairment	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) • Fluid retention (edema, heart failure) • Benefit in NASH • ↑ Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide: use cautiously; initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality associated with use of sulfonylureas (glibenclamide)
Insulin – Human Insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	• Lower insulin doses required with renal decrease in eGFR; titrate per clinical response	• Injection site reactions • Risk of severe hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – Analogs						High	SQ			

Note. Reprinted from *Standards of medical care in diabetes – 2018 abridged for primary care providers*, by American Diabetes Association (2018), retrieved from http://clinical.diabetesjournals.org/content/36/1/14.full-text.pdf Copyright 2018 by American Diabetes Association.

Mechanism of Action of Sulfonylureas and GLP-1s

Table 2

Antidiabetic medication class specifics for GLP-1s and SUs

Class	Agents (Route of Administration)	Cellular Mechanism (s)	Primary Physiologic Action(s)	Advantages	Disadvantages	Cost
GLP-1 RAs	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide Lixisenatide (SC injection)	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some CV risk factors • Associated with lower CVD event rate and mortality in patients with CVD	• GI side effects (nausea, vomiting, diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
SUs	Second generation Glimepiride Glipizide Glyburide (oral)	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk • Relatively higher HbA1c efficacy	• Hypoglycemia • ↑ Weight	Low

Note. CV = cardiovascular; CVD = cardiovascular disease; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; SC = subcutaneous SU = sulfonylurea; XR = extended release. Adapted from *Pharmacologic approaches to glycemic treatment*, by American Diabetes Association (2017), retrieved from http://professional.diabetes.org/content/clinical-practice-recommendations Copyright 2017 by American Diabetes Association.

Literature Review

Benefits of GLP-1s and Sulfonylureas in the Treatment of Uncontrolled T2DM

Chou et al. (2017)

- Lower risk of myocardial infarcts when taking GLP-1s as compared to those taking sulfonylureas (OR = 0.48; 95% CI [0.27, 0.91]).
- GLP-1s decrease several cardiovascular risk factors such as body weight, weight circumference, and blood pressure.
- Limitations: only randomized controlled trials available in English with less than one year follow-up.

Courtney, Nayar, Rajeswaran, and Jandhyala (2017)

- DURATION-1 study was able to show decrease in A1c (0.4-1.7%) and weight loss (0.9-5.3 kg) with long term treatment using a GLP-1.
- Only 4-21% of those that discontinued treatment of GLP-1s was due to adverse effects which tend to dissipate with continued treatment.
- Limitations: Types of studies reviewed and lack of comparison of two GLP-1s.

Courtney et al. (2017)

- LEADER trial: GLP-1 (liraglutide) was compared against a placebo which demonstrated cardiovascular benefit from the GLP-1 with fewer deaths from cardiovascular causes, nonfatal myocardial infarction, or nonfatal strokes (95% CI [0.78, 0.97]; $p = 0.01$).
  - A1c dropped by 0.4% in those treated with the GLP-1 (95% CI [-0.5, -0.3]).
  - Weight loss dropped by 2.3 kg more using GLP-1 treatment (95% CI, [2.0-2.5]).
- ELIXA trial: Evaluated the cardiovascular benefits of lixisenatide (GLP-1).
  - No significant difference in lixisenatide versus placebo (13.4% vs. 13.2%) was found regarding cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina (95% CI [0.89-1.17]; $p = 0.81$).

Risks of GLP1s and Sulfonylureas in the Treatment of Uncontrolled T2DM

Table 3

Adverse events when adding or switching to sulfonylureas

Exposure	No of patients	No of events	Person years	Incidence rate (95% CI) per 1000 person years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Myocardial infarction						
Adding sulfonylureas	13 203	57	11 442	5.0 (3.8 to 6.5)	Reference	Reference
Switching to sulfonylureas	9759	68	5138	13.2 (10.4 to 16.8)	2.65 (1.86 to 3.78)	1.51 (1.03 to 2.24)
Ischaemic stroke						
Adding sulfonylureas	13 300	63	11 §42	5.5 (4.3 to 7.0)	Reference	Reference
Switching to sulfonylureas	9771	46	5185	8.9 (6.6 to 11.8)	1.60 (1.09 to 2.34)	0.88 (0.58 to 1.33)
Cardiovascular death						
Adding sulfonylureas	13 217	75	11 464	6.5 (5.2 to 8.2)	Reference	Reference
Switching to sulfonylureas	9779	93	5204	17.9 (14.6 to 21.9)	2.70 (1.99 to 3.66)	1.22 (0.87 to 1.71)
All cause mortality						
Adding sulfonylureas	13 242	217	11 504	18.9 (16.5 to 21.5)	Reference	Reference
Switching to sulfonylureas	9800	256	5216	49.1 (43.4 to 55.5)	2.57 (2.14 to 3.08)	1.23 (1.00 to 1.50)
Severe hypoglycaemia						
Adding sulfonylureas	13 215	39	11 440	3.4 (2.5 to 4.7)	Reference	Reference
Switching to sulfonylureas	9770	45	5177	8.7 (6.5 to 11.6)	2.61 (1.70 to 4.01)	1.06 (0.65 to 1.71)

*The models for myocardial infarction, ischaemic stroke, cardiovascular death, and severe hypoglycaemia were adjusted for age, sex, deciles of propensity score, history of the respective outcome in the year before cohort entry (or, for the case of cardiovascular death, history of myocardial infarction or ischaemic stroke), body mass index category, diuretics, statins, paracetamol, opioids, and nephropathy. The model for all cause mortality was adjusted for age, sex, deciles propensity score, body mass index category, diuretics, statins, paracetamol, opioids, and nephropathy.

Reprinted from "Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: Population based cohort study", by A. Douros, S. Dell'Aniello, O. Yu, K.B. Filion, L. Azoulay and S. Suissa, 2018, *BMJ, 362*, p. 8. Copyright 2018 by The BMJ.

- Limitations to this study include a short duration of follow up and the fact that drug doses were not considered.

Discussion

- First line treatment: diet and exercise
- If not effective, the addition of metformin is recommended.
- Chou et al. (2017), Courtney et al. (2017), and Maruthur et al. (2016) report the benefits of GLP-1s include decreased cardiovascular risk factors by decreasing weight and blood pressure.
- Choby (2017) provides cost information identifying sulfonylureas to be more affordable than GLP-1s. The affordability of medication plays a role in selecting an antidiabetic drug for different patient populations.
- Currently, sulfonylureas are available as oral medications as opposed to GLP-1s that are only available in the injectable form. GLP-1s are offered in daily or once weekly dosing options. The route of administration may affect prescribing patterns depending on patient preference.
- Gastrointestinal side effects (nausea, vomiting, and diarrhea) are the most commonly reported adverse effects in those who use GLP-1s. Avoiding GLP-1s in patient's with a history of pancreatitis is recommended.

Discussion

- Choby (2017) and Maruthur et al. (2016) stated hypoglycemia and weight gain as the most reported adverse effects of sulfonylureas. Douros et al. (2018) indicate an increased risk of myocardial infarction, all cause mortality, and severe hypoglycemia with sulfonylureas when compared to metformin monotherapy.
- Maruthur et al. (2016) reported on three randomized controlled trials (n = 2,557) with an odds ratio of 3.4-7.1 and a risk difference of 15-30%. The combination of metformin and GLP-1 is favored over a metformin and sulfonylurea combination with a moderate strength of evidence in supporting effectiveness.
- Overall, the review of literature demonstrates benefits of GLP-1s over sulfonylureas. The adverse effects of GLP-1s may decrease with length of treatment while adverse effects of sulfonylureas remain unchanged. The cost, gastrointestinal side effects, and method of administration of GLP-1s be a deterrent for patients.

Applicability to Clinical Practice

- In clinical practice, T2DM is a diagnosis that is encountered almost daily in the primary care setting.
- New treatment options continue to be developed to improve the management of adults with T2DM.
- Between the dosage of medication, class of medication, adverse effects, and affordability of the medications, it may take multiple clinic visits to be obtain diabetic control before the possibility of the body changing and needing to find the necessary balance again.
- Benefits of GLP-1s: weight loss, low risk of hypoglycemia, decrease in systolic blood pressure, and cardiovascular protective benefits.
- Risks of GLP-1s: gastrointestinal side effects are the largest drawback and potentially the biggest cause for discontinuation of this treatment, higher cost, and method of administration (injectable).
- Benefits of sulfonylureas: effective at lowering A1c, lower cost, method of administration (oral).
- Risks of sulfonylureas: weight gain, hypoglycemia when utilized as a monotherapy and to a less extent as a combination therapy with metformin.
- With the future of genetic research, the potential to predict the effectiveness or lack of effectiveness of different medications for patients may dramatically change the prescribing patterns for providers treating T2DM.

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